55, 108, 109, 115, 129, and 160 are amended as above. No new claims are added. No new matter is added to the Specification by these changes.

I. Withdrawal of claims. In examining the claims, the Examiner has taken the position that an immune system must be an immune system *in vivo*, and therefore has rejected certain claims (claims 109, 111-112, 115-116, 122-123, 125-126, 129, 136-139, 142-150, 153-156, 160-175, 184-185, and 188-191) as incomplete for omitting an essential step (see discussion below), and has withdrawn certain claims (claims 50-55, 60, 63-66, 79-81, 84-91, 94-97, 102-104, and 108) as being drawn to a non-elected invention, also because they lack an administering step. Applicant respectfully challenges the Examiner's positions and requests substantive examination of the excluded claims. A Petition for Withdrawal of Finality related to this invention is enclosed.

With respect to the definition of "immune system", Applicant respectfully submits that the present specification makes clear that this term can refer to an *in vivo* or an *in vitro* response. The case law is quite clear that a patentee may be his own lexicographer, as long as the meaning of the word is not repugnant to the usual meaning of the term (MPEP 2173.05(a), *In re Hill* 161 F.2d 367, 73 USPQ 482 (CCPA 1947)). In this case, the Specification clearly contemplates both *in vivo* and *ex vivo* immune responses. For example, in the Definition section (page 12, line 7), a primary immune response is defined as referring to the initial activation of immune system cells when they encounter or recognize a particular antigen for the first time. There is no requirement in this definition that the cells be *in vivo*. Furthermore, at page 24, line 5, the Specification includes an entire section devoted to "Modulation of pAPC/Antigen Encounter *ex vivo*". The first sentence of this section, "in certain preferred embodiments of the invention, control over immune response is exerted by modulation of a pAPC/antigen encounter *ex vivo* (*e.g.*, *in vitro*)," provides ample support for the Applicant position regarding the instant claims and specifically the definition of the term "immune system".

Rather than considering the clear meaning set forth in the Specification, the Examiner has cited a textbook by Janeway *et al.* and has taken the position that this textbook defines an immune system as an *in vivo* system. Applicant respectfully submits, firstly, that claim terms are properly defined by reference to the specification rather than extrinsic sources and, secondly, that

the Janeway *et al.* textbook is *not* limited to *in vivo* systems. Specifically, the cited portion of the textbook describes immune system as "the molecules, cells, organs, and processes involved in host defense against infection." Nothing in this definition is limited to *in vivo*. Surely, the molecules, cells , and processes (and possibly even the organs) involved in host defense can be isolated and studied *in vitro*. In fact, the Janeway *et al.* reference itself describes using "methodologies from biochemistry, molecular biology, cell biology, physiology, pathology, and microbiology" to study the immune system. Clearly, most of these methodologies are employed *in vitro*. Applicant therefore respectfully submits that the Examiner's definition of "immune system" is unduly narrow and not consistent with either the specification or the general literature. Thus, the elected claims are drawn to a method of modulating an immune response, to an antigen, whether that response occurs *in vivo* or *in vitro*. Claims lacking an administration step should not be excluded from consideration.

Applicant requests that the instant claims be examined in light of the Applicant's intended definition of immune system as disclosed in the Specification and not using the definition of Janeway *et al.* Applicant respectfully submits that the claims are complete as written and that the step of administering the cells to a subject is not essential. Also, given the argument above, Applicant submits that claims 50-55, 60, 63-66, 79-81, 84-91, 94-97, 102-104, and 108 should not have been withdrawn by the Examiner as being drawn to a non-elected invention. These are in fact drawn to the elected invention, and Applicant requests examination of these claims and a withdrawal of finality since the Examiner did not act on these claims in the last Office Action.

Furthermore, Applicant respectfully submits that the Examiner is improperly relying on the preamble of the claim to limit its scope. The scope of a method claim is defined by the recited steps; the claim would have the same scope even if there were no preamble other than "A method comprising steps of: . . . ". Applicant therefore sumbits that currently-pending claim 50 is identical in scope to orginally-filed claim 50 and therefore cannot be patentably distinct; the withdrawal of claims 50-55, 60, 63-66, 79-81, 84-91, 94-97, 102-104, and 108 from consideration should be removed.

Applicant respectfully requests reexamination and reconsideration of the case, as amended. Each of the rejections levied in the Office Action is addressed individually below.

II. Rejection under 35 U.S.C. §112, second paragraph, as being indefinite. Claims 109, 111-112, 115-116, 122-123, 125-126, 129, 136-139, 142-150, 153-156, 160-175, 184-185, and 188-191 stand rejected under 35 USC §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, Examiner argues that claims 109, 111-112, 115-116, 122-123, 125-126, 129, 136-139, 142-150, 153-156, 160-175, 184-185, and 188-191 are incomplete for omitting essential steps, such as "administering isolated and exposed pAPC to a subject so as to modulate an immune response."

Applicant respectfully disagrees. As discussed above, the term "immune system" in the present specification and claims is not limited to an *in vivo* immune system. There is no logical gap in the recited steps in the present claims, and no essential step is omitted. Those of ordinary skill in the art would readily appreciate the metes and bounds of the claim.

III. Rejection under 35 U.S.C. §103(a). All examined claims 109, 111-112, 115-116, 122-123, 125-126, 129, 136-139, 142-150, 153-156, 160-175, 184-185, and 188-191 stand rejected under 35 USC §103(a) as being unpatentable over U.S. Patent 5,994,126 in view of WO98/37919 and Romagnani ("The Th1/Th2 paradigm" *Immunology Today* 18(6):263-266, June 1997) and others. Applicant previously argued that there is no motivation to combine the cited references to render the presently claimed invention obvious. In responding to Applicant's argument, the Examiner does not point to any motivation within the cited references, but rather offers the conclusory statement that "in this case, the use of a well known adjuvant/immunomodulator (CpG) to direct an immune response in a particular well known direction (towards Th1), said response including the direction/modulation of a well known cell type (dendritic cells), is not unobvious." Applicant respectfully submits that the Examiner has not established a *prima facie* case of obviousness because a clear and particular showing of a suggestion, teaching, or motivation to combine prior teachings has not been given. The Federal Circuit in ***In re Dembiczak*** (175 F.3d 994, 50 USPQ2d 1614 (Fed. Cir. 1999)) ruled that a showing of a suggestion, teaching, or motivation to combine prior teachings "must be clear and particular . . . . Broad conclusory statements regarding the teaching of multiple references,

standing alone, are not 'evidence.'" If the Examiner wishes to maintain that there is a suggestion to combine the cited references, the Applicant requests that the Examiner clearly and particularly identify the suggestion, teaching, or motivation *in the cited references*; otherwise, the Applicant respectfully requests that the rejection be removed.

Applicant further argued previously that, even if there were motivation to combine the cited references to try and achieve the claimed invention, there would be no reasonable expectation of success. The Examiner did not respond to this argument other than to say "Neither is the expectation of success unreasonable". The Examiner gave no support for his assertion that the teachings of cited references could be applied to different cells than described in the cited references, to achieve a different result. Applicant respectfully submits that the Examiner has not established a reasonable expectation of success.

Furthermore, Applicant notes that, in order to further prosecution of the present claims toward allowance, the independent claims 109 and 160 have been amended to recite "allergic antigen". Support for such an amendment can be found throughout the application, for example, on page 16, starting at line 6 in the discussion of allergy. None of the cited references has any teaching or suggestion of the invention recited in these amended claims. Specifically, the references do not teach or suggest the use of allergic antigens, and further do not teach the use of allergic antigens to modulate the immune response away from a Th2 response.

Without a suggestion to combine the references and to use allergic antigens in modulating the response away from a Th2 response, the Applicant submits that a *prima facie* case of obvious has not been established, and therefore, requests that the rejection be removed.

In view of the forgoing arguments, Applicant respectfully submits that the present case is now in condition for allowance. A Notice to that effect is requested.

Please charge any fees that may be required for the processing of this Response, or credit any overpayments, to our Deposit Account No. 03-1721.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner For Patents, Washington, D.C. 20231
on April 5, 2001
Karen E. Lopes

50. A method of modulating an immune system response to an antigen, the method comprising steps of:

isolating from an individual one or more pAPC selected from the group consisting of: mature pAPC, immature pAPC, and precursors to pAPC; and

exposing the isolated cells to an allergic antigen so that pAPC displaying the antigen are generated, and a pre-determined set of cytokines is expressed.

51. The method of claim 50, further comprising:

administering the antigen-exposed pAPC to a subject whose immune response to the antigen is to be modulated.

52. The method of claim 50, wherein:

the antigen-exposed pAPC are mature pAPC.

53. The method of claim 50, wherein:

the antigen-exposed pAPC are immature pAPC.

54. The method of claim 50, wherein:

the pAPC are selected from the group consisting of dendritic cells, B cells, and macrophages.

55. The method of claim 50, wherein:

the pAPC are dendritic cells.

60. The method of claim 50, wherein:

the step of exposing the isolated cells to an antigen comprises exposing the cells to a crude antigen preparation.

61. The method of claim 50, wherein:

the step of exposing the isolated cells to an antigen comprises exposing the cells substantially pure antigen.

63. The method of claim 50, wherein:

the step of exposing the cells to antigen comprises contacting the cells with an antigen that is associated with a targeting agent.

64. The method of claim 50, wherein:

the step of exposing the isolated cells to an antigen further comprises exposing the cells to a composition comprising a factor selected from the group consisting of cytokines and inducing agents, which factor is selected to bias an immune response in a subject away from a Th1 or a Th2 response in a pre-determined manner.

65. The method of claim 64, wherein:

the step of exposing comprises exposing the cells to one or more Th1 inducing agents.

66. The method of claim 65, wherein:

the Th1 inducing agents are selected from the group consisting of LPS, CD40, CD40 ligand, BCGs, oligonucleotides containing CpG motifs, TNFα, and microbial extracts.

67. The method of claim 66, wherein:

the microbial extracts are selected from the group consisting of any *Staphylococcus aureus* preparation, heat killed *Listeria,* and modified cholera toxin.

68. The method of claim 64, wherein:

the cytokines comprise Th1 stimulatory cytokines.

69. The method of claim 68, wherein:

the cytokines are selected from the group consisting of IL-12, IL-2, IL-18, IL-1ß, fragments of IL-1ß, IFNα, and IFNγ.

79. The method of claim 64, wherein:
the one or both of the antigen and factor are associated with a targeting agent.

80. The method of claim 79, wherein:
the association with the targeting agent occurs by means of an interaction selected from the group consisting of covalent bonds, hydrogen bonds, van der Waals interactions, hydrophobic interactions, and combinations thereof.

81. The method of claim 79, wherein:
the targeting agent is selected from the group consisting of mannose receptor ligand and the Fc receptor ligand.

82. The method of claim 79, wherein:
the targeting agent comprises complement receptor ligand.

83. The method of claim 79, wherein:
the targeting agent comprises DEC205.

84. The method of claim 79, wherein:
the targeting agent is capable of targeting to intracellular vesicles within pAPCs.

85. The method of claim 79, wherein:
the targeting agent comprises at least the Fc portion of an Ig molecule.

86. The method of claim 79, wherein:
the targeting agent comprises at least the Fc portion of an IgG molecule.

N.G 87. The method of claim 50, wherein:
the antigen is encapsulated.

N.C 88. The method of claim 64, wherein:
the step of exposing comprises providing the antigen and factor together in an encapsulation device.

N-C 89. The method of claim 64, wherein:
the step of exposing comprises providing the antigen and the factor in separate encapsulation devices.

N.C 90. The method of claim 87, 88, or 89, wherein:
the step of exposing comprises exposing the cells to the encapsulation device in association with a targeting agent.

N.C 91. The method of claim 90, wherein:
the targeting agent is selected from the group consisting of mannose receptor ligand and the Fc receptor ligand.

N.C 92. The method of claim 90, wherein:
the targeting agent comprises complement receptor ligand.

N.C 93. The method of claim 90, wherein:
the targeting agent comprises DEC205.

N.C 94. The method of claim 90, wherein:
the targeting agent is capable of targeting to particular vesicles within pAPCs.

N.C 95. The method of claim 90, wherein:
the targeting agent comprises at least the Fc portion of an Ig molecule.

96. The method of claim 90, wherein:

the targeting agent comprises at least the Fc portion of an IgG molecule.

97. The method of claim 64, wherein:

the step of exposing comprises providing antigen and factor that are associated with one another by means of an interaction selected from the group consisting of: covalent bonds, hydrogen bonds, van der Waals interactions, hydrophobic interactions, and combinations thereof.

98. The method of claim 50, wherein:

the step of exposing the antigen comprises exposing the cells to a modified antigen.

102. The method of claim 64, wherein:

the antigen comprises an allergen; and

the factor is selected to bias the immune response to the antigen away from a Th2 response.

103. The method of claim 102, wherein:

the factor comprises a Th1 inducing agent.

104. The method of claim 102, wherein:

the factor is selected from the group consisting of LPS, CD40, CD40 ligand, BCGs, oligonucleotides containing CpG motifs, TNFα, and microbial extracts.

105. The method of claim 104, wherein:

the microbial extracts are selected from the group consisting of any *Staphylococcus aureus* preparation, heat killed *Listeria,* and modified cholera toxin.

106. The method of claim 51, wherein:

the step of administering further comprises administering a cytokine selected from the group consisting of Th1 stimulatory cytokines and Th2 stimulatory cytokines to the subject.

107. The method of claim 106, wherein:

the Th1 stimulatory cytokines are selected from the group consisting of IL-12, IL-2, IL-18, IL-1ß, fragments of IL-1ß, IFNα, and IFNγ and the Th2 stimulatory cytokines are selected from the group consisting of IL-4.

108. The method of claim 50, further comprising:

administering antigen to the subject.

109. A method of modulating an immune system response to an antigen, the method comprising steps of:

isolating from an individual one or more APC selected from the group consisting of: mature pAPC, immature pAPC, and precursors of pAPC;

exposing the isolated cells to an allergic antigen so that mature pAPC displaying the antigen are generated; and

contacting the antigen-exposed pAPC with T cells so that a pre-determined T-cell response is inhibited.

110. The method of claim 109, wherein:

the step of exposing is performed under conditions selected so that mature pAPC displaying antigen is a produced and a pre-determined set of cytokines, selected from the group consisting of Th1 cytokines and Th2 cytokines, is expressed.

111. The method of claim 109 wherein:

the pre-determined T cell response is selected from the group consisting of: a Th1 response and a Th2 response.

112. The method of claim 111, wherein:

the Th1 or Th2 response is inhibited through induction of an opposing Th2 or Th1 response.

115. The method of claim 109, wherein:

the step of contacting comprises contacting the antigen exposed pAPC with T cells in the presence of a Th1 inducing agent, so that the expression of one or more Th1 cytokines is induced and Th2 response is inhibited in the T cells.

116. (Amended) The method of claim 109, wherein:

the step of contacting comprises contacting the antigen-exposed pAPC with T cells in the presence of a Th1 inducing agent selected from the group consisting of LPS, CD40, CD40 ligand, BCGs, oligonucleotides containing CpG motifs, THFα, and microbial extracts, so that the expression of one or more Th1 cytokines is induced and a Th2 response is inhibited in the T cells.

117. The method of claim 116, wherein:

the microbial extracts are selected from the group consisting of any *Staphylococcus aureus* preparation, heat killed *Listeria,* and modified cholera toxin.

122. The method of claim 109, wherein:

the pAPC are selected from the group consisting of dendritic cells, B cells, and macrophages.

123. The method of claim 109, wherein:

the pAPC are dendritic cells.

125. The method of claim 123, wherein:

the step of maturing is performed concurrently with the step of exposing to antigen.

126. The method of claim 109, wherein:

the step of exposing the isolated cells to an antigen comprises exposing the cells to a crude antigen preparation.

127. The method of claim 109, wherein:

the step of exposing the isolated cells to an antigen comprises exposing the cells to substantially pure antigen.

129. The method of claim 109, wherein:

the step of exposing further comprises exposing the cells to a factor selected from the group consisting of cytokines and inducing agents.

136. The method of claim 109 wherein:

the antigen is provided in association with a targeting agent.

137. The method of claim 129, wherein:

one or both of the antigen and factor is provided in association with a targeting agent.

138. The method of claim 136 or claim 137, wherein:

the association with the targeting agent occurs by means of an interaction selected from the group consisting of covalent bonds, hydrogen bonds, van der Waals interactions, hydrophobic interactions, and combinations thereof.

139. The method of claim 136 or claim 137, wherein:

the targeting agent is selected from the group consisting of mannose receptor ligand and the Fc receptor ligand.

140. The method of claim 136 or claim 137, wherein:

the targeting agent comprises complement receptor ligand.

141. The method of claim 136 or claim 137, wherein:

the targeting agent comprises DEC205.

142. The method of claim 136 or claim 137, wherein:
the targeting agent is capable of targeting to particular vesicles within pAPCs.

143. The method of claim 136 or claim 137, wherein:
the targeting agent comprises at least the Fc portion of an Ig molecule.

144. The method of claim 143, wherein:
the targeting agent comprises at least the Fc portion of an IgG molecule.

145. The method of claim 109, wherein:
the step of exposing comprises providing the antigen in an encapsulation device.

146. The method of claim 129, wherein:
one or both of the antigen and factor is encapsulated.

147. The method of claim 129, wherein:
the antigen and factor are provided together as a single composition.

148. The method of claim 147, wherein:
the antigen and factor are provided encapsulated together in a single encapsulation device.

149. The method of claim 145, 146, or claim 148, wherein:
the encapsulation device is associated with a targeting agent.

150. The method of claim 149, wherein:
the targeting agent is selected from the group consisting of mannose receptor ligand and the Fc receptor ligand.

151. The method of claim 149, wherein:
the targeting agent comprises complement receptor ligand.

152. The method of claim 149, wherein:
the targeting agent comprises DEC205.

153. The method of claim 149, wherein:
the targeting agent is capable of targeting to intracellular vesicles within pAPCs.

154. The method of claim 149, wherein:
the targeting agent comprises at least the Fc portion of an Ig molecule.

155. The method of claim 149, wherein:
the targeting agent comprises at least the Fc portion of an IgG molecule.

156. The method of claim 129, wherein:
the step of exposing comprises providing antigen and factor that are associated with one another by means of an interaction selected from the group consisting of: covalent bonds, hydrogen bonds, van der Waals interactions, hydrophobic interactions, and combinations thereof.

157. The method of claim 109, wherein:
the step of exposing the antigen comprises exposing the cells to a modified antigen.

160. A method of treating allergy, the method comprising steps of:
identifying an individual who is allergic to an allergic antigen;
providing a composition of pAPC displaying the antigen; and
contacting the composition with T cells of the individual under conditions that inhibit a Th2 response to the antigen.

161. The method of claim 160, wherein:

the pAPC are selected for their expression of Th1 cytokines.

162. The method of claim 160, wherein:

the pAPC are selected from the group consisting of dendritic cells, B cells, and macrophages.

163. The method of claim 161, wherein:

the pAPC are dendritic cells.

164. The method of claim 160, wherein:

the step of providing comprises:

isolating from an individual one or more cells selected from the group consisting of mature pAPC, immature pAPC, and precursors to pAPC; and

exposing the isolated cells to the antigen.

165. The method of claim 164, wherein:

the step of exposing the isolated cells to the antigen further comprises exposing the isolated cells to a factor selected from the group consisting of cytokines and inducing agents.

166. The method of claim 165, wherein:

the factor comprises an inducing agent that induces expression of one or more Th1 stimulating cytokines in the pAPC.

167. The method of claim 165 wherein:

the antigen and factor are provided together as part of a single composition.

168. The method of claim 165, wherein:

one or both of the antigen and factor is associated with a targeting agent.

169. The method of claim 164, wherein:
the antigen is associated with a targeting agent.

170. The method of claim 167, wherein:
the antigen and factor are encapsulated together in an encapsulation device.

171. The method of claim 164, wherein
the antigen is encapsulated.

172. The method of claim 165, wherein:
one or both of the antigen and factor is encapsulated.

173. The method of claim 165, wherein:
the antigen and factor are both encapsulated.

174. The method of claim 173, wherein:
the encapsulation device is associated with a targeting agent.

175. The method of claim 164, wherein:
the step of exposing the isolated cells to antigen comprises exposing the cells to a crude preparation of antigen.

176. The method of claim 164, wherein:
the step of exposing the isolated cells to an antigen comprises exposing the cells substantially pure antigen.

184. The method of any one of claims 168, 169, or 174, wherein:
the association with the targeting agent occurs through an interaction selected from the group consisting of covalent bonds, hydrogen bonds, van der Waals interactions, hydrophobic interactions, and combinations thereof.

185. The method of any one of claims 168, 169, or 174, wherein:

the targeting agent is selected from the group consisting of mannose receptor ligand and the Fc receptor ligand.

186. The method of any one of claims 168, 169, or 174, wherein:

the targeting agent comprises complement receptor ligand.

187. The method of any one of claims 168, 169, or 174, wherein:

the targeting agent comprises DEC205.

188. The method of any one of claims 168, 169, or 174, wherein:

the targeting agent is capable of targeting to intracellular vesicles within pAPCs.

189. The method of any one of claims 168, 169, or 174, wherein:

the targeting agent comprises at least the Fc portion of an Ig molecule.

190. The method of any one of claims 168, 169, or 174, wherein:

the targeting agent comprises at least the Fc portion of an IgG molecule.

191. The method of claim 175, wherein:

the step of exposing comprises providing antigen and factor that are associated with one another by means of an interaction selected from the group consisting of: covalent bonds, hydrogen bonds, van der Waals interactions, hydrophobic interactions, and combinations thereof.

192. The method of claim 164, wherein:

the step of exposing the antigen comprises exposing the cells to a modified antigen.

193. The method of claim 192, wherein:

the modified antigen is substantially identical to a naturally-occurring antigen that contains at least one IgE binding site except that the modified antigen lacks at least one of the IgE binding sites.